



Armed Forces College of Medicine AFCM



Diabetes Mellitus (Integrated Lecture 1)

Integrated Departments



- **Histology:** Prof. Manal Hassan
- **Biochemistry:** Assist.Prof. Magy maher
- **Pathology:** Prof. Nermeen Salah
- **Internal medicine:** Assist.Prof. Dr. Nesma Ali
- **Pharmacology:** Prof. Omayma Khorshid

Intended Learning Outcomes (ILOs)



By the end of this lecture the student will be able to:

- 1** Describe the microscopic structure of the cells in the islets of Langerhans (Histology)
- 2** Correlate the structure of the islet cells with their function
- 3** Mention the paracrine regulatory effect between the cells in islets of Langerhans (Histology)
- 4** Explain biochemical basis of diabetes mellitus and its symptoms (Bio)
- 5** Describe the pathological features of pancreas in DM and its complications (Pathology)
- 6** Diagnosis of diabetes mellitus (Internal Medicine)
- 7** Classification of diabetes mellitus (Internal Medicine)
- 8** Screening for type 2 diabetes (Internal Medicine)
- 9** Prevention of type 2 diabetes (Internal Medicine)
- 10** Identify Routes of administration of Insulin Preparations (Pharmacology)
- 11** Compare the pharmacokinetic profiles of common Insulin Preparations (Pharmacology)

Diabetes Mellitus



2015



One in 11 adults has diabetes

2040



One in 10 adults will have diabetes

Top 10 countries for number of adults with diabetes



Rank	Country/territory	2015 Number of people with diabetes
1	China	109.6 million (99.6-133.4)
2	India	69.2 million (56.2-84.8)
3	United States of America	29.3 million (27.6-30.9)
4	Brazil	14.3 million (12.9-15.8)
5	Russian Federation	12.1 million (6.2-17.0)
6	Mexico	11.5 million (6.2-13.7)
7	Indonesia	10.0 million (8.7-10.9)
8	Egypt	7.8 million (3.8-9.0)
9	Japan	7.2 million (6.1-9.6)
10	Bangladesh	7.1 million (5.3-12.0)

Rank	Country/territory	2040 Number of people with diabetes
1	China	150.7 million (138.0-179.4)
2	India	123.5 million (99.1-150.3)
3	United States of America	35.1 million (33.0-37.2)
4	Brazil	23.3 million (21.0-25.9)
5	Mexico	20.6 million (11.4-24.7)
6	Indonesia	16.2 million (14.3-17.7)
7	Egypt	15.1 million (7.3-17.3)
8	Pakistan	14.4 million (10.6-20.4)
9	Bangladesh	13.6 million (10.7-24.6)
10	Russian Federation	12.4 million (6.4-17.1)

Histology of Pancreas

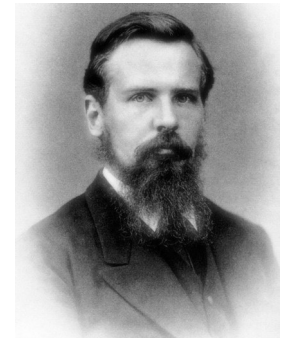
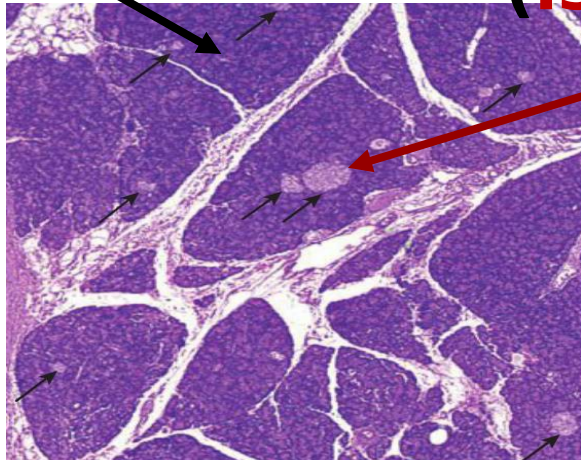


Pancreas



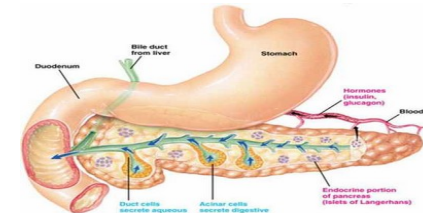
**Exocrine
portion**

**Endocrine portion
(islets of Langerhans)**

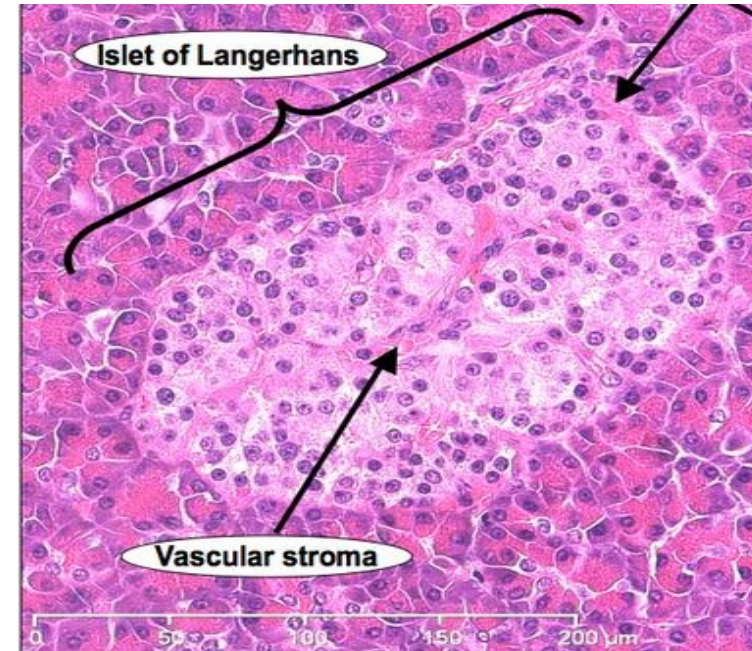


Histology atlas and test: Michael H.
Ross and Wojciech Pawlina, 7th
edition, 2015. Fig 18-22
Endocrine & genitourinary module

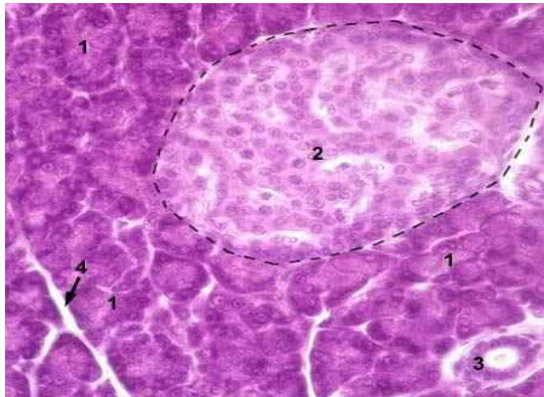
Pancreas: Islets of Langerhans



- Site: mainly in the tail.
- Pale area surrounded by the deeply stained acini
- Structure:
branched cords of **polygonal or rounded cells** separated by **fenestrated blood capillaries**.



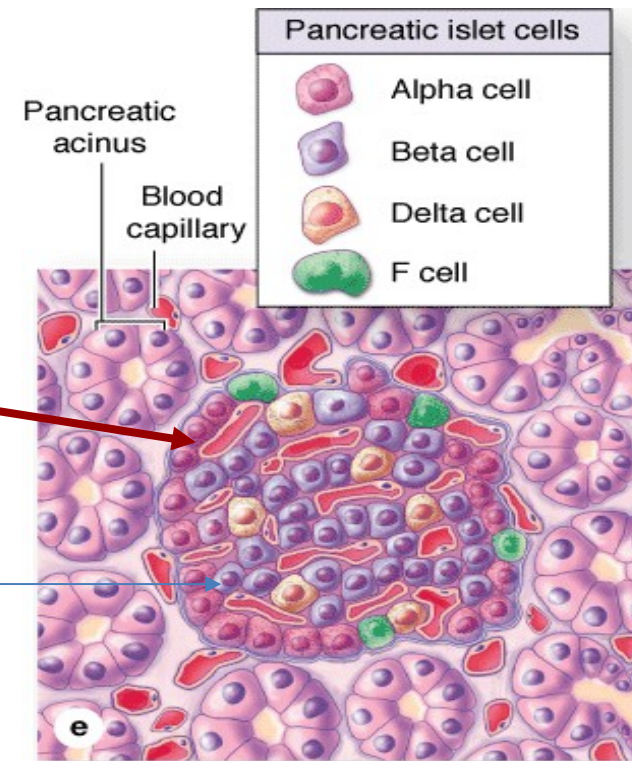
Pancreas: Islets of Langerhans



LM: different grades of **basophilia** **α -cells**

EM: They are all protein secreting cells containing:

- Rough endoplasmic reticulum **β cells**
- Golgi apparatus
- Secretory granules that vary in size and density from cell to cell



differentiated by immunohistochemistry

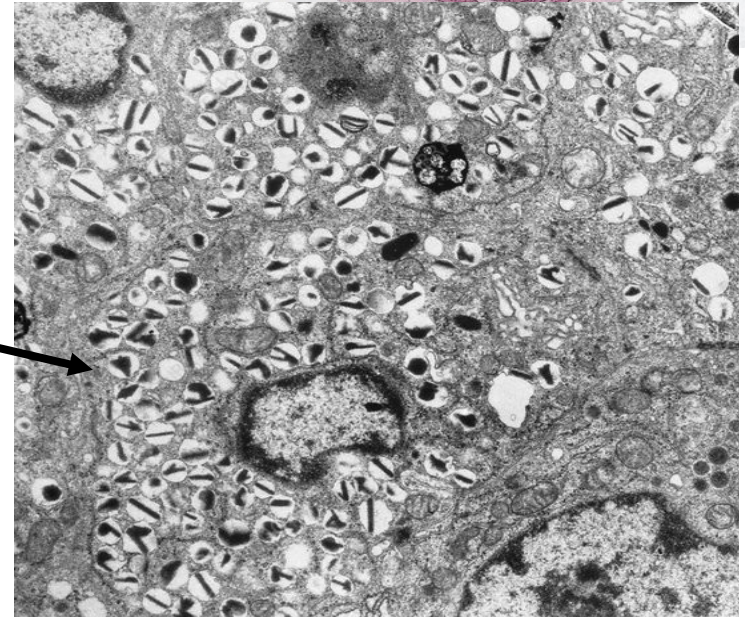
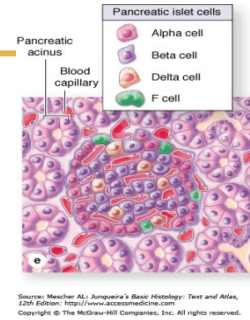
Source: Mescher AL: *Junqueira's Basic Histology: Text and Atlas*, 12th Edition. <http://www.accessmedicine.com>
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Pancreas: Islets of Langerhans: β beta cells

- 70 %
- Situated mainly **centrally**
- Relatively **small**

EM:-----, numerous secretory granules with dense polyhydral core and a pale matrix. The polyhedral core is believed to be crystallized insulin.

Function: Secrete **insulin**



Pancreas: Islets of Langerhans: **A alpha cells**

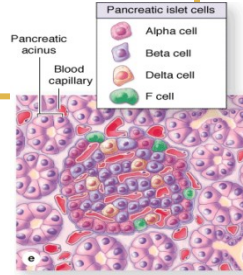
- **20 %**
- Situated mainly **peripherally**
- Relatively **large**

EM: -----, secretory granules more

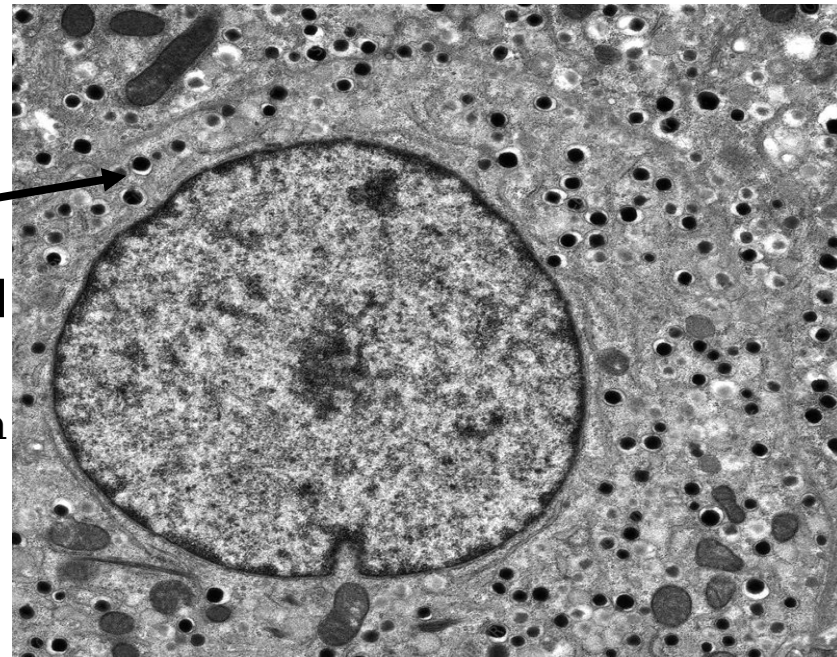
uniform in size and more densely packed in the cytoplasm than the granules of B

cells with electron dense core surrounded by a clear area

Function: Secrete glucagon



Source: Mescher AL, Junqueira's Basic Histology: Text and Atlas, 12th Edition. <http://www.accessmedicine.com>
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<https://www.sciencephoto.com/media/891865/view>

Pancreas: Types of cells in Islets of Langerhans



Cell	%	Site in the islet	structure	Hormone produced	Function
Alpha cells α-cells	20 %	Peripheral	Large cell, uniform granules	Glucagon	Increase blood glucose level (glycogenolysis)
Beta cells β cells	70 %	Central	Small cell, dense core granules	Insulin	Decrease blood glucose level
D cells δ cells	5%	Peripheral	Large secretory granules with lower electron density	Somatostatin	Inhibitory Inhibits release of other islet cell hormones by local paracrine action
F (PP) cells	1%			Pancreatic polypeptide	Inhibit secretion of pancreatic enzymes, Stimulates activity of gastric chief cells:

Control of Islets of Langerhans



1- **Blood glucose** level

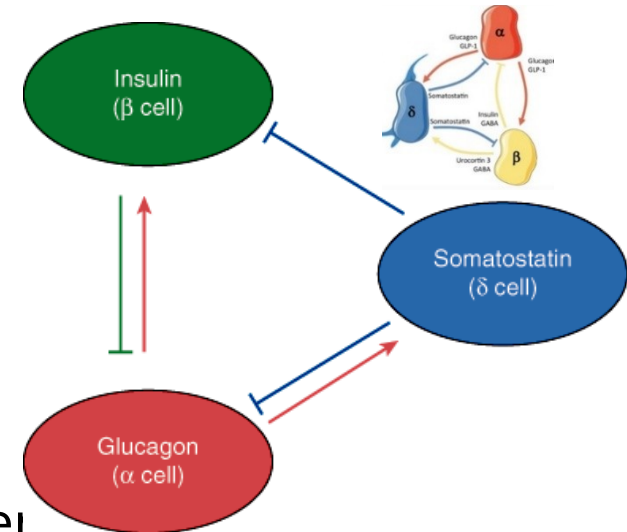
2- **Paracrine regulation**

Insulin (-) **release**
of glucagon.

Glucagon (+) **insulin &**
somatostatin.

3- **Gap junction** **Somatostatin** (-) **insulin &**
glucagon.

transfer the autonomic neural stimulus to the other cells



Diabetes Mellitus



Diabetes is not one disease, but rather is a heterogeneous group of syndromes characterized by an elevation of fasting blood glucose caused by a relative or absolute deficiency in insulin.

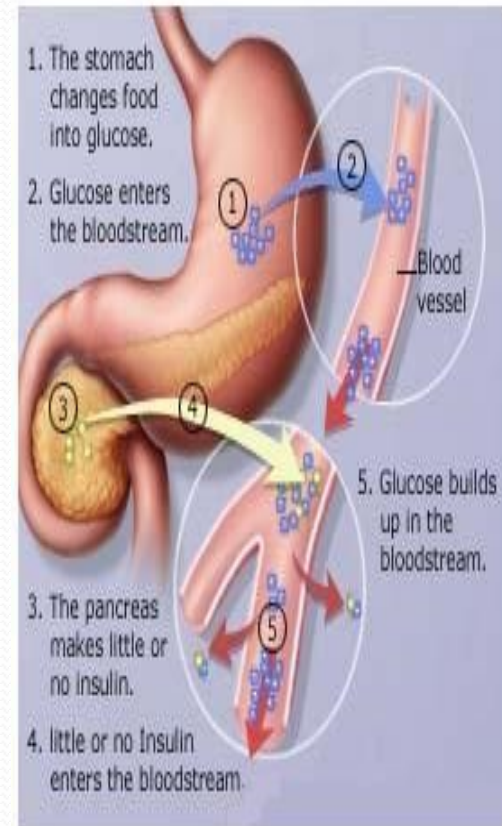


Disturbance in carbohydrate, lipid, protein and mineral metabolism.

Diabetes Mellitus



Blood glucose levels are controlled by a complex interaction of multiple chemicals and hormones in the body, including the **insulin** hormone made in the **beta cells** of the pancreas .

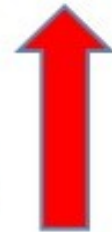


Hormones Involved in Regulation of blood glucose

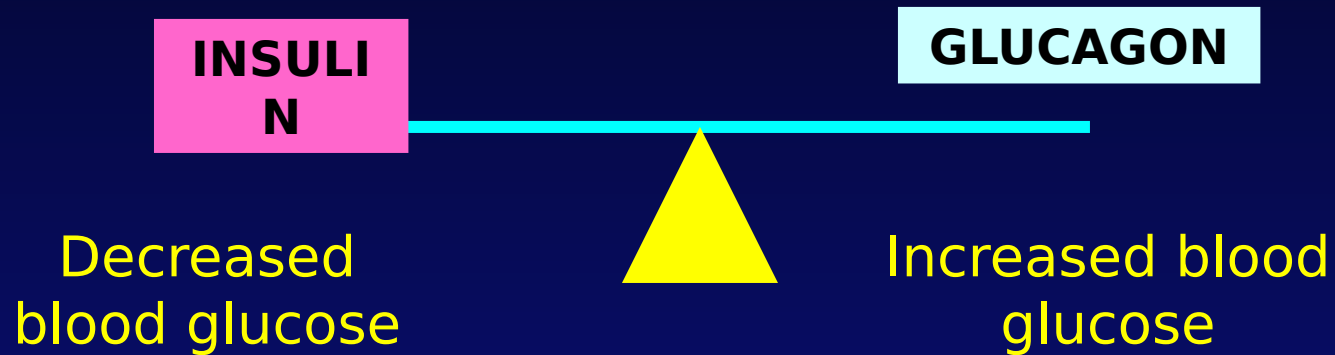
- **DECREASE Blood Glucose**
- **Insulin**
- **Somatostatin**



- **INCREASE Blood Glucose**
- **Glucagon**
- **Epinephrine**
- **Cortisol**
- **ACTH**
- **Growth Hormone**
- **Thyroxine**



INSULIN-GLUCAGON RELATIONSHIPS

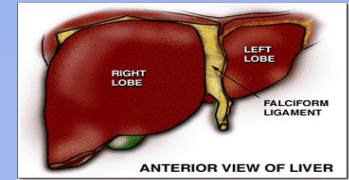




**Insulin
insufficiency**



**Reduced tissue
uptake of glucose**



**Intracellu
l
hypoglyce
mia**

**Extracellu
l
hyperglyce
mia**

Signs and Symptoms of DM



- 1- Polyuria.**
- 2- Polydypsea.**
- 3- Polyphagia.**
- 4- Loss of weight.**
- 5- Dehydration.**
- 6- Glucosuria.**

Why ? ?

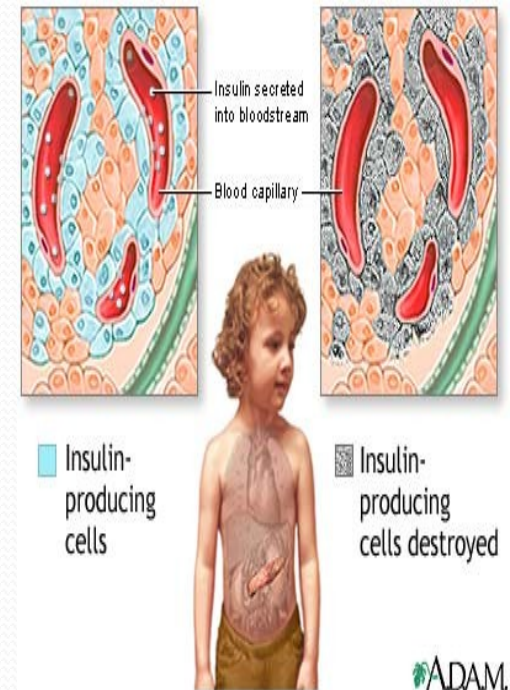
- Glycosuria: glucose excretion in urine and due to osmotic effect, more water accompanies the glucose (polyuria).
- To compensate for this loss of water, thirst center is activated & more water is taken (polydypsia).
- To compensate the loss of glucose & protein, patient will take more food (polyphagia).

Type I Diabetes

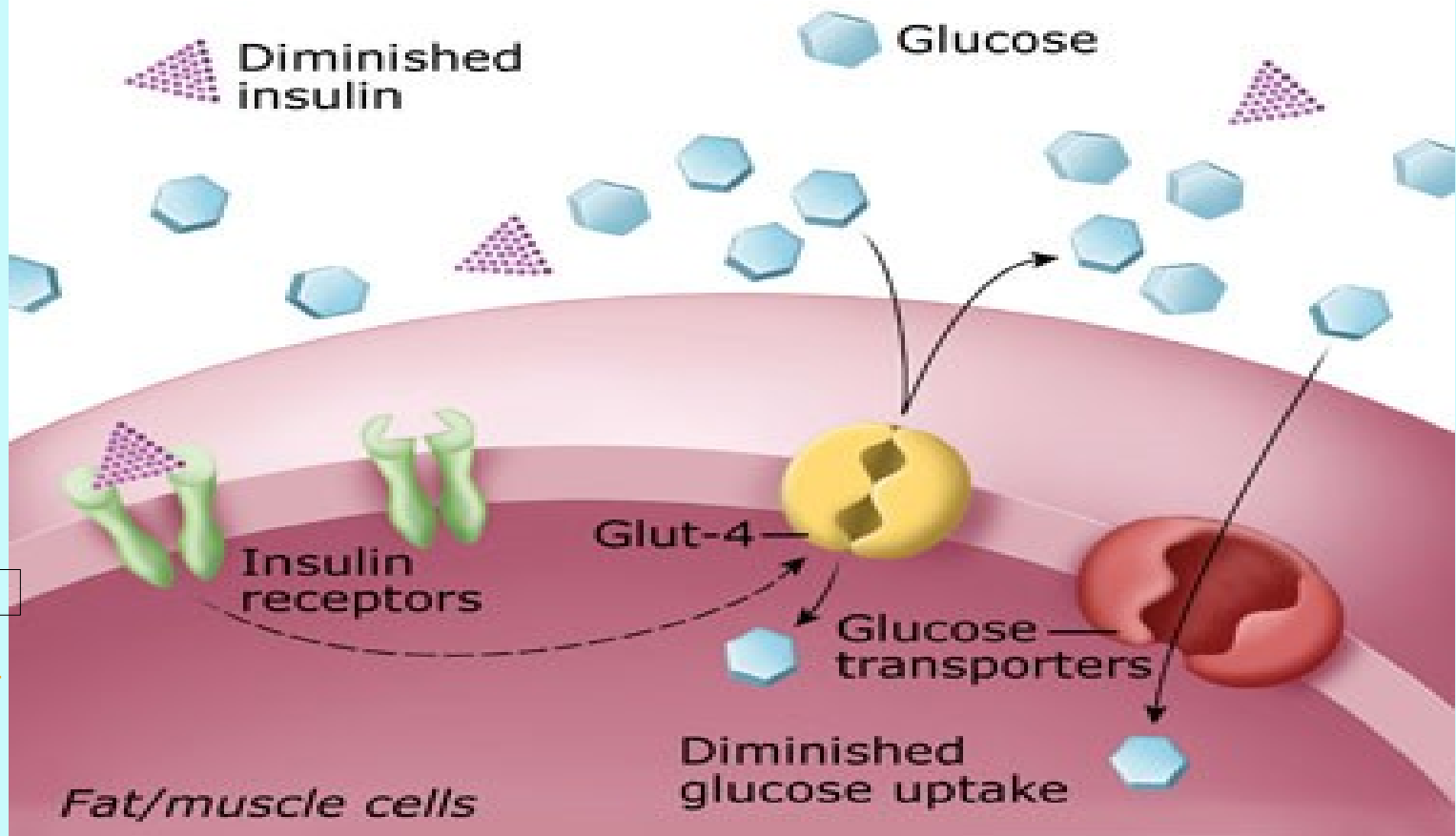


Type I Diabetes

- ❖ It constitutes about **10%** of diabetics.
- ❖ Characterized by **absolute deficiency of insulin** caused by **an autoimmune attack on β cells** of the pancreas
- ❖ Symptoms appear suddenly when **80-90%** of the cells are destroyed.



Type 1 Diabetes: Insufficient Insulin

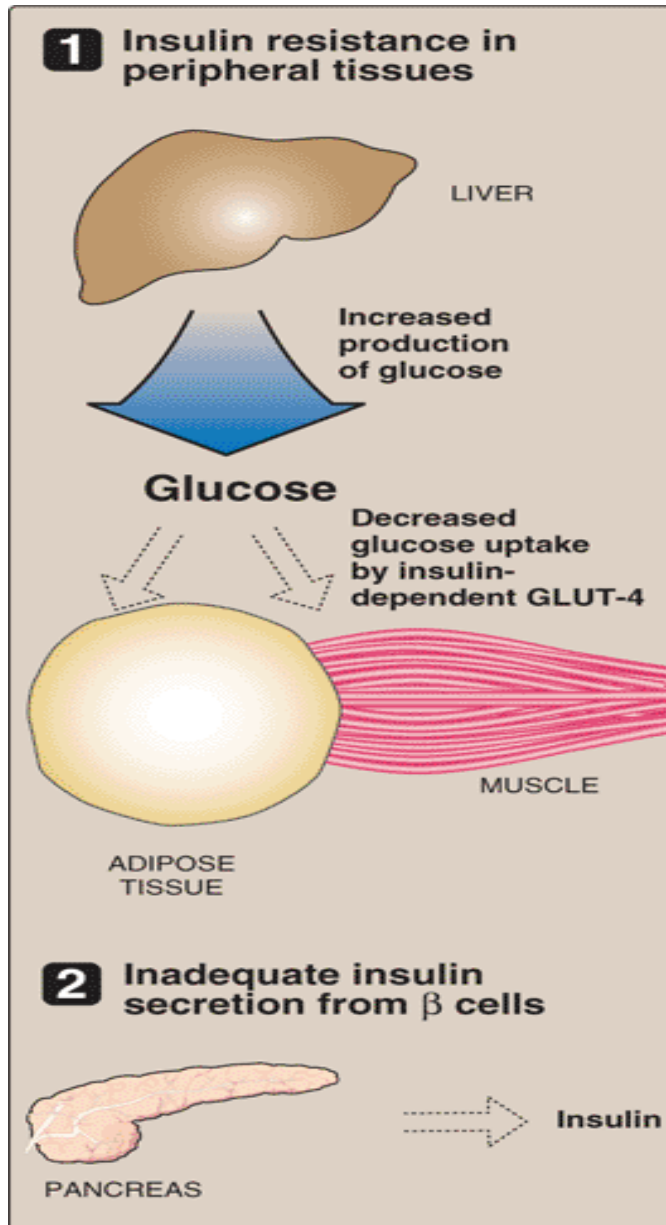


<https://www.slideshare.net/shahjadaselim9/pathophysiology-and-classification-of-diabetes-by-dr-selim>

Type II Diabetes

Type II Diabetes

- It represents around **90%** of the diabetic population.
- Type II diabetes develops gradually and sometimes detected by routine screening.
- Patients have a combination of **insulin resistance & dysfunctional β - cells.**
- Metabolic changes are milder than type I and ketoacidosis is a rare complication.

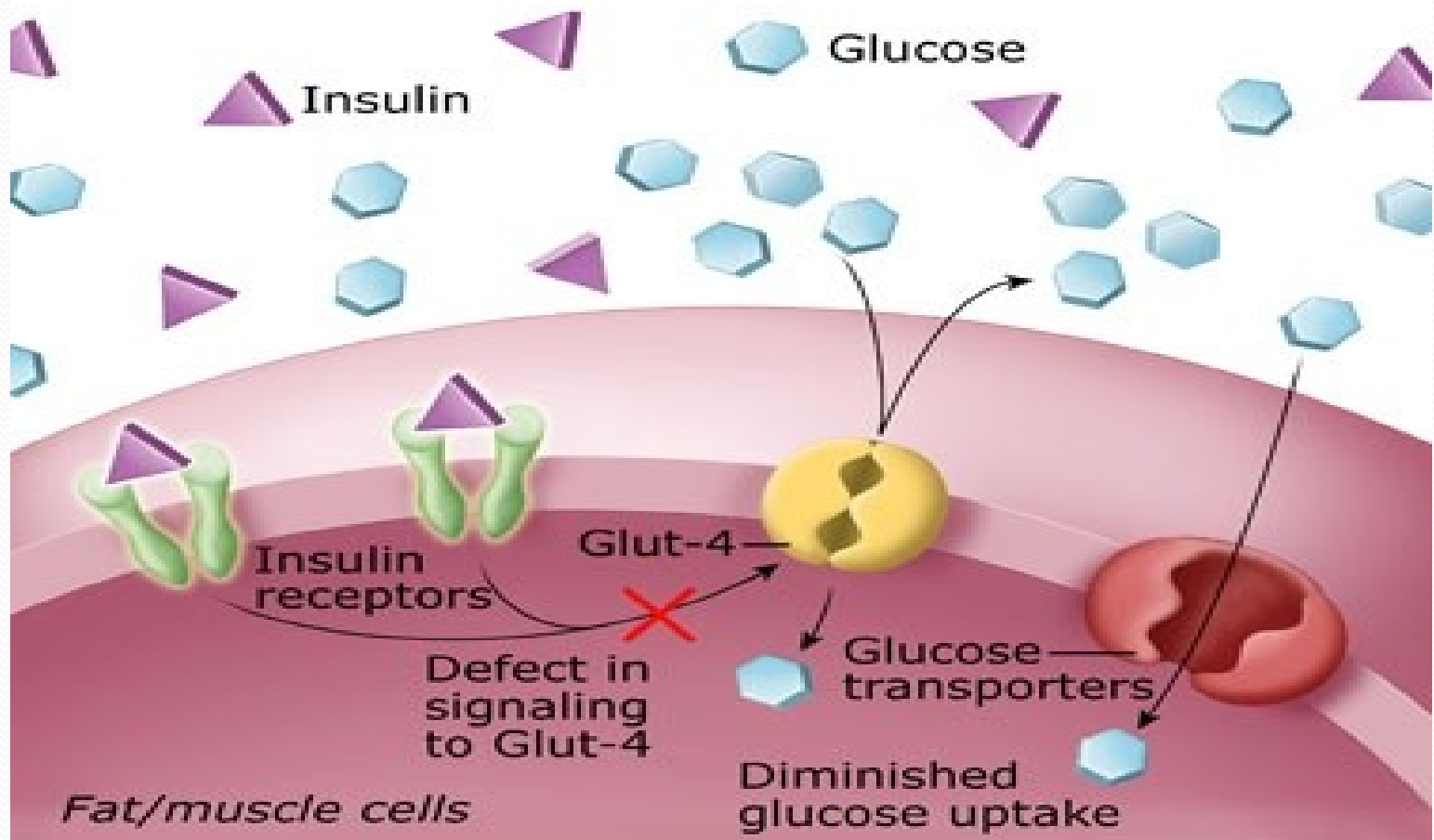


A-Insulin resistance: it is the decreased ability of target tissues e.g. adipose and muscle to respond properly to normal circulating insulin levels.

B- Insulin resistance alone does not lead to it but a defect in β -cell function as well.

Harper's Illustrated Biochemistry-29th edition.

Type 2 Diabetes: Insulin Resistance



<https://research.halkidiabetesremedy.org/?hop=zainescu>

Dysfunctional β -cells

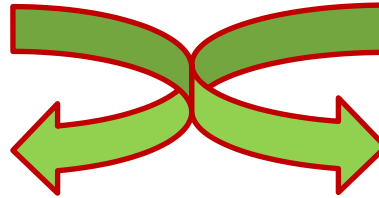
- In type II diabetes, the pancreas initially retains β -cell capacity to secrete insulin.
- However, with time, the β - cells become increasingly dysfunctional and fail to secrete enough insulin to correct hyperglycemia.

Pathology



Pathology of the pancreas in DM

Gross



Secondary DM



Pancreas shows gross features of the causative disease

Primary DM



Pancreas looks normal

DM

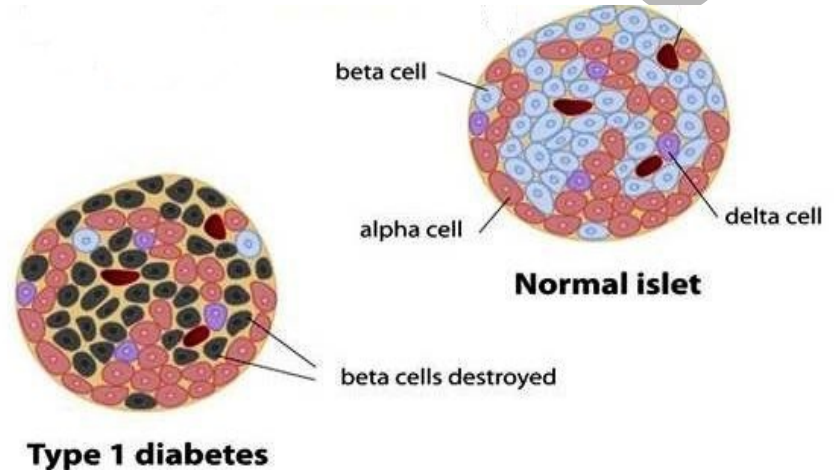


,Microscopically :Secondary DM

It shows the specific lesions leading to pancreatic destruction

:Primary DM

- ❑ Reduction in number & size of islets of Langerhans
(**Most often in type 1 diabetes**)
- ❑ Amyloid replacement of islets in long standing **type 2 diabetes**
- ❑ Leucocytic infiltration of islets
in both types



Pathogenesis of long term complications in diabetes



Persistent **hyperglycaemia** is the key mediator
Complications are due to the following mechanisms

1-Formation of advanced glycation end products (AGEs) responsible for

- ❑ **Atherosclerosis** acceleration (help LDL to be trapped in vessel wall)
- ❑ Basement membrane thickening

2-Activation of intracellular protein kinase C :Production of

- ❑ **VEGF**

leading to neovascularization seen in diabetic retinopathy

- ❑ **TGF-B**

leading to increased *deposition of extracellular matrix*

Complications of DM



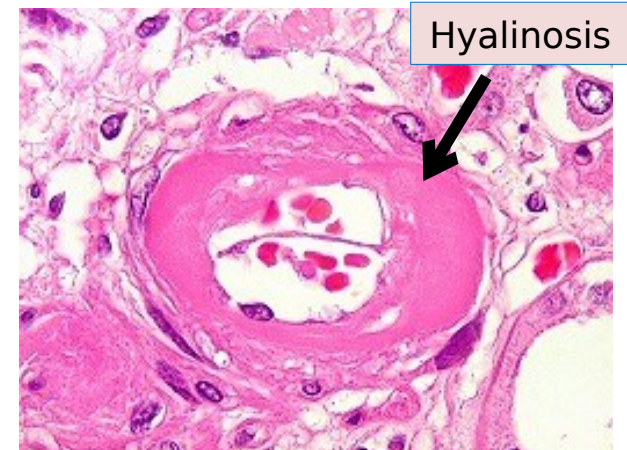
1-Vascular lesions :

A) Microangiopathy:

- ❑ **Diffuse thickening of basement membranes** (d.t AGEs & TGF- B) in **capillaries** by hyaline material composed predominantly of collagen type IV
- ❑ Despite thickening of BM, diabetic capillaries are more leaky than normal to plasma protein
- ❑ It leads to ischemia & low immunity , nephropathy, neuropathy & retinopathy

B) Hyaline arteriolosclerosis:

Hyaline thickening of wall of arterioles with narrowing of lumen due to associated hypertension
(leakage of plasma components across vascular endothelium)



C) Atherosclerosis with superimposed thrombosis → *Myocardial infarction

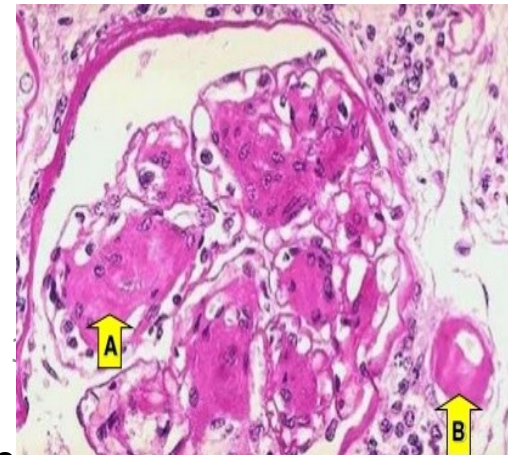
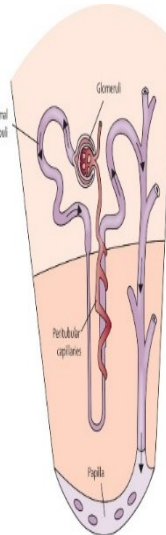
*Cerebral ischemia *Diabetic

Complications of DM



2-Renal lesions: Diabetic nephropathy

- ❑ **Pyelonephritis** and **papillary necrosis**
- ❑ **Atherosclerosis** of renal artery
- ❑ **Hyaline arteriosclerosis** of afferent and efferent arterioles
- ❑ **Glomerulosclerosis** in long standing diabetes for 12 years or more Take TWO forms
 - **Diffuse glomerulosclerosis** in which there is **diffuse increase in mesangial matrix with diffuse thickening of glomerular basement membrane (microangiopathy)** → loss of protein in urine (**nephrotic syndrome**)
 - **Nodular glomerulosclerosis**(**kimmelstiel Wilson lesion**)



A: Nodular glomerulosclerosis.
B: Hyaline Arteriosclerosis.

Complications



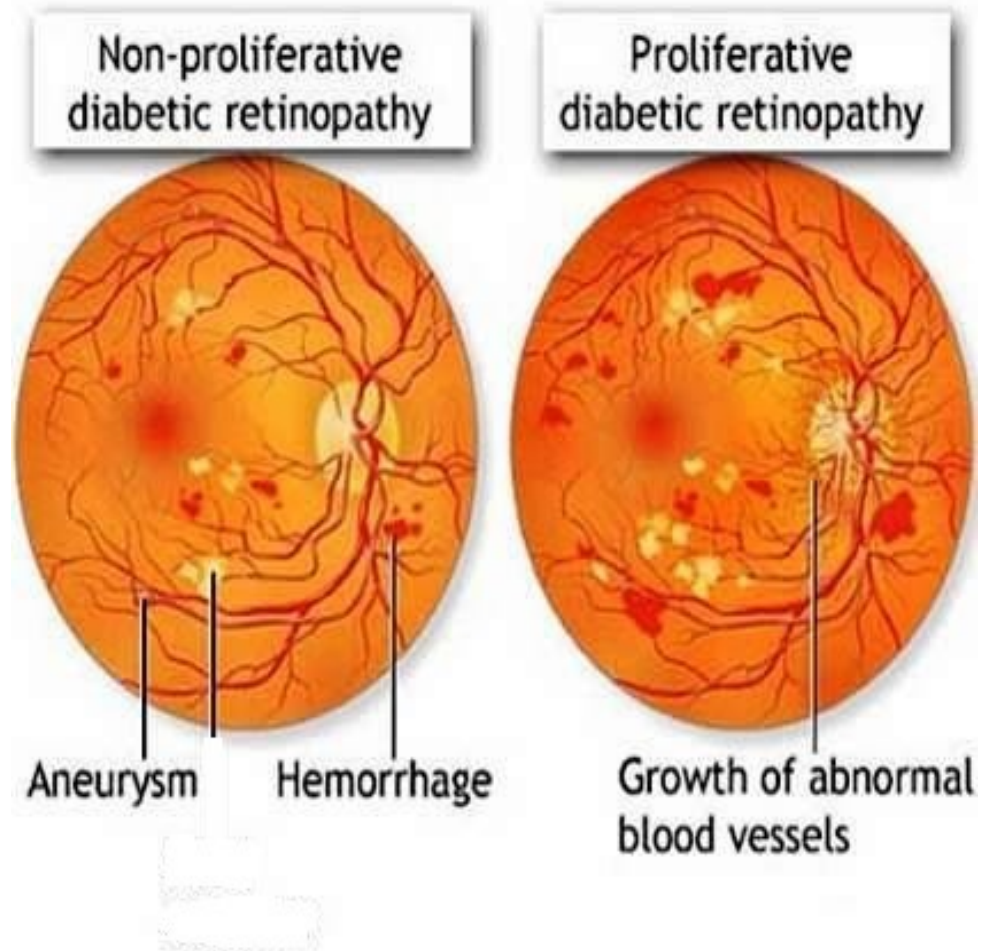
Retinopathy-3

:A) Non proliferative

Retina shows
microangiopathy,
microaneurysms, retinal
exudates, edema and
minute hemorrhage

:B) Proliferative

Retina shows
neovascularization
Retinal hemorrhage and
organization → retinal
detachment → **blindness**



Complications

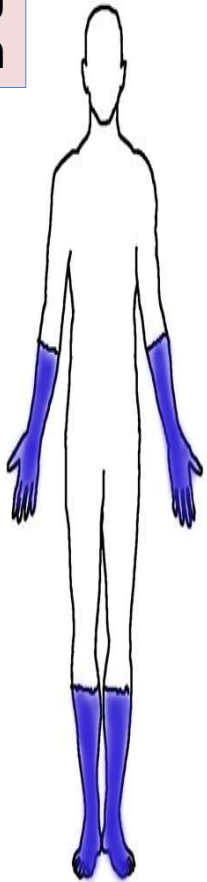


4-Nervous system

❑ Peripheral neuropathy

- It symmetrically affects distal extremities
- both motor and sensory functions are affected

Glove and stocking distribution



5- Increases susceptibility to Infections

Due to

- Impaired leucocyte functions, defect in migration
- Reduced cellular immunity
- Poor blood supply due to vascular involvement
- Hyperglycemia

Pathology department

Clinical Aspects of Diabetes Mellitus



Classification



1. **Type 1** diabetes (results from b-cell destruction, usually leading to absolute insulin deficiency)
2. **Type 2** diabetes (results from a progressive insulin secretory defect on the background of insulin resistance)
3. **Other specific types** of diabetes
4. **Gestational** diabetes mellitus (GDM) (diabetes diagnosed during pregnancy)

Classification

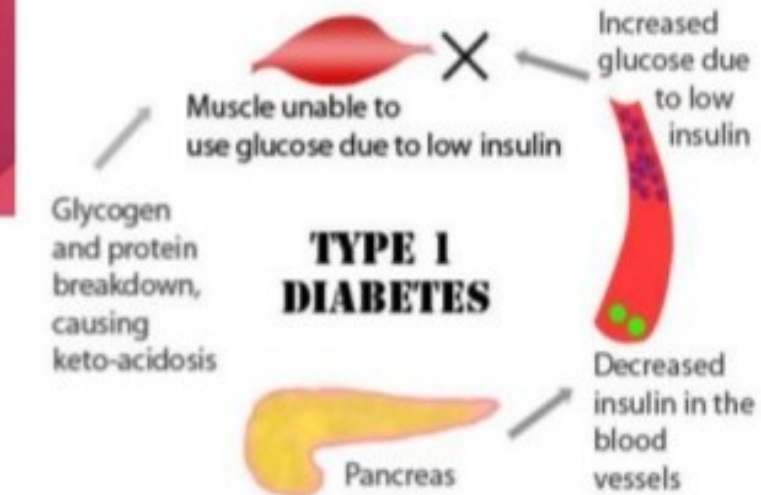


❑ **Other specific types of diabetes:**

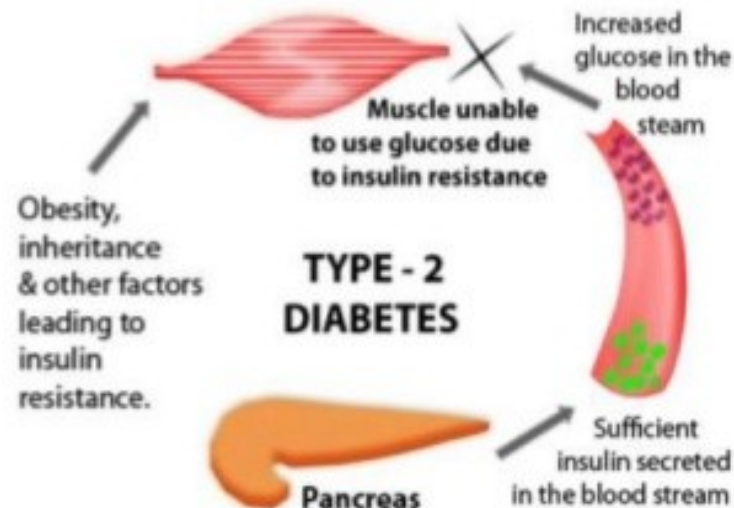
1. Genetic defects in b-cell function
2. Genetic defects in insulin action
3. Diseases of the exocrine pancreas (such as cystic fibrosis)
4. Drug- or chemical induced (such as in the treatment of HIV/AIDS or after organ transplantation)

Type 1 DM results from the body's failure to produce enough insulin. This form was previously referred to as "insulin-dependent diabetes mellitus" (IDDM) or "juvenile diabetes". The cause is unknown.

Type 2 DM begins with **insulin resistance**, a condition in which cells fail to respond to insulin properly. As the disease progresses a lack of insulin may also develop.¹ This form was previously referred to as "non



Type 2 Diabetes



Clinical Manifestations



- Polyuria
- Polydipsia
- Polyphagia
- Weight loss, weakness and fatigue
- Recurrent infection, prolonged wound healing
- Altered immune and inflammatory response, prone to infection (e.g; genital pruritus)

Diagnosis of DM



Table 2.1—Criteria for the diagnosis of diabetes

FPG ≥ 126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 h.*

OR

2-h PG ≥ 200 mg/dL (11.1 mmol/L) during an OGTT. The test should be performed as described by the WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.*

OR

A1C $\geq 6.5\%$ (48 mmol/mol). The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.*

OR

In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥ 200 mg/dL (11.1 mmol/L).

*In the absence of unequivocal hyperglycemia, results should be confirmed by repeat testing.

Diagnosis of DM



- If two different tests (such as A1C and FPG) are both above the diagnostic thresholds, the diagnosis of diabetes is confirmed
- If the results of two different tests are discordant, the test whose result is above the diagnostic cut point should be repeated, and the diagnosis is made on the basis of the confirmed test.

Laboratory evaluation



- **A1C**, if results not available within past 2–3 months
- If not performed/available within past year:
 - Fasting **lipid** profile: total, LDL, HDL cholesterol TG
 - **Liver** function tests
 - Test for urinary albumin excretion with spot urine albumin/creatinine
 - Serum **creatinine** and calculated **GFR**
 - Thyroid-stimulating hormone in:
 - type 1 diabetes
 - Dyslipidemia
 - women over age 50 years

Risk factors and screening



Diabetes mellitus is a lab diagnosis ,
but the issue is how to identify the risk
group for screening (that is our job).



DIABETES: A GLOBAL VIEW

TYPE 2 DIABETES RISK FACTORS

Family history
of diabetes



Overweight



Unhealthy
diet



Physical
inactivity



Increasing
age



High blood
pressure



Ethnicity



Higher than normal
blood glucose



History of
gestational diabetes



Poor nutrition
during pregnancy

Screening for Type 2 diabetes



Table 2.3—Criteria for testing for diabetes or prediabetes in asymptomatic adults

1. Testing should be considered in overweight or obese ($\text{BMI} \geq 25 \text{ kg/m}^2$ or $\geq 23 \text{ kg/m}^2$ in Asian Americans) adults who have one or more of the following risk factors:
 - $\text{A1C} \geq 5.7\%$ (39 mmol/mol), IGT, or IFG on previous testing
 - first-degree relative with diabetes
 - high-risk race/ethnicity (e.g., African American, Latino, Native American, Asian American, Pacific Islander)
 - women who were diagnosed with GDM
 - history of CVD
 - hypertension ($\geq 140/90 \text{ mmHg}$ or on therapy for hypertension)
 - HDL cholesterol level $< 35 \text{ mg/dL}$ (0.90 mmol/L) and/or a triglyceride level $> 250 \text{ mg/dL}$ (2.82 mmol/L)
 - women with polycystic ovary syndrome
 - physical inactivity
 - other clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans).
2. For all patients, testing should begin at age 45 years.
3. If results are normal, testing should be repeated at a minimum of 3-year intervals, with consideration of more frequent testing depending on initial results (e.g., those with prediabetes should be tested yearly) and risk status.



Table 2.4—Categories of increased risk for diabetes (prediabetes)*

FPG 100 mg/dL (5.6 mmol/L) to 125 mg/dL (6.9 mmol/L) (IFG)

OR

2-h PG in the 75-g OGTT 140 mg/dL (7.8 mmol/L) to 199 mg/dL (11.0 mmol/L) (IGT)

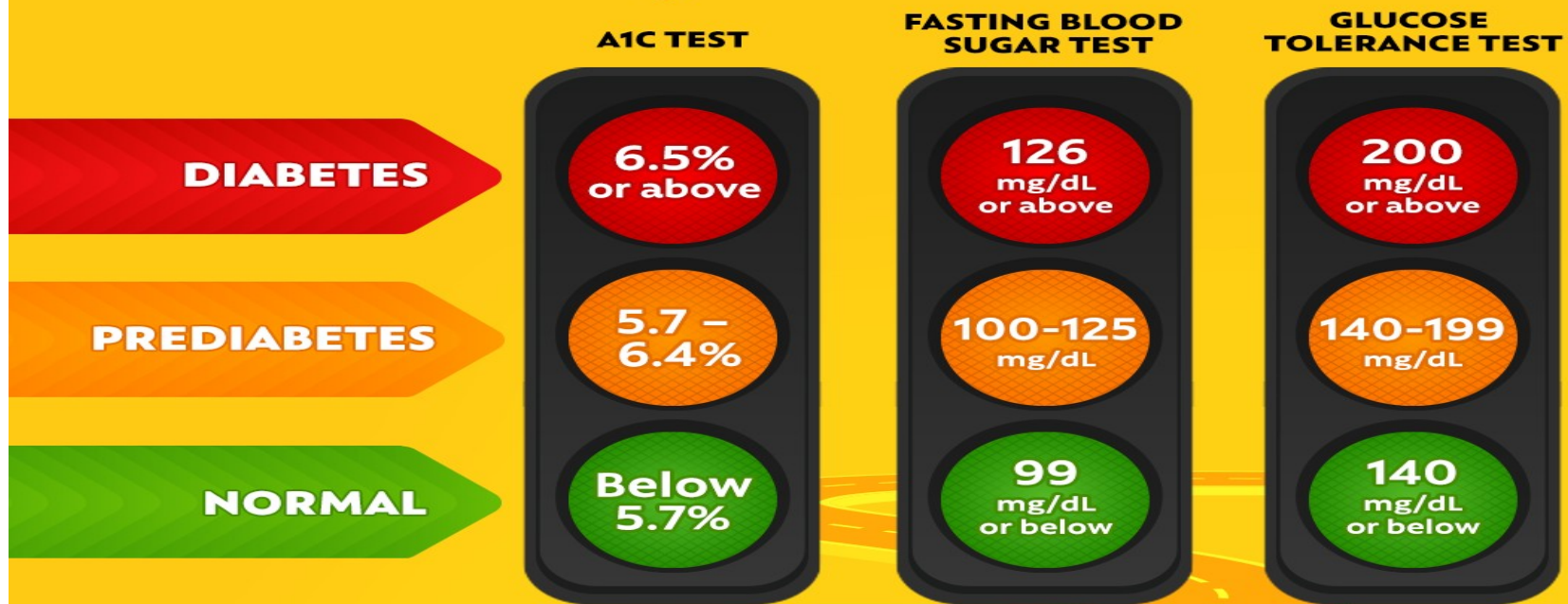
OR

A1C 5.7–6.4% (39–47 mmol/mol)

*For all three tests, risk is continuous, extending below the lower limit of the range and becoming disproportionately greater at the higher end of the range.



THE ROAD TO TYPE 2 DIABETES



Source: American Diabetes Association



Diabetes treatment and prevention



Prevention/delay of type 2 diabetes



- Patients with prediabetes should be referred to Diabetes Prevention Program (DPP):
 -
 - an intensive diet → loss of 7% of body weight
 - physical activity → increase their moderate-intensity physical activity (such as brisk walking) to at least 150 min/week.
 - behavioral counseling program
- Follow-up counseling and maintenance programs should be offered for long-term success in preventing diabetes.
- Based on the cost-effectiveness of diabetes prevention, such programs should be covered by

Prevention/delay of type 2 diabetes



- **Metformin** for prevention of type 2 diabetes should be considered in those with prediabetes, especially with:
 - BMI > 35 kg/m²,
 - aged < 60 years,
 - women with prior gestational diabetes mellitus.
- At least annual monitoring for the development of diabetes in those with prediabetes.

Prevention/delay of type 2 diabetes



- Screening for and treatment of **modifiable risk factors** for cardiovascular disease is suggested.
- **Diabetes self-management education** and support programs can prevent or delay the onset of diabetes.
- **Technology-assisted tools** (Internet-based social networks, distance learning, DVD-based content, and mobile applications) can be useful for effective lifestyle modification to prevent diabetes.

Non-pharmacological approaches for diabetes treatment



- Dietary modifications
- Smoking cessation
- Reduce alcohol intake
- Take up regular moderate exercise
- Avoid obesity or lose weight if obese

Pharmacological



A collection of various medical supplies is arranged on a white surface. In the upper right, a blue pill bottle is tipped over, spilling several light blue oval pills. To its left, a purple and white capsule and a white oval pill are visible. In the center, a clear glass vial with a blue cap is partially visible. To the right, a clear glass vial with a white cap is also partially visible. In the lower right, a syringe with a clear barrel and an orange plunger is shown, with a white oval pill resting on its barrel. A yellow oval pill is also visible near the syringe. In the lower left, a yellow oval pill is visible. The background is a plain white surface.

Antidiabetic c Drugs

Insulin Preparations

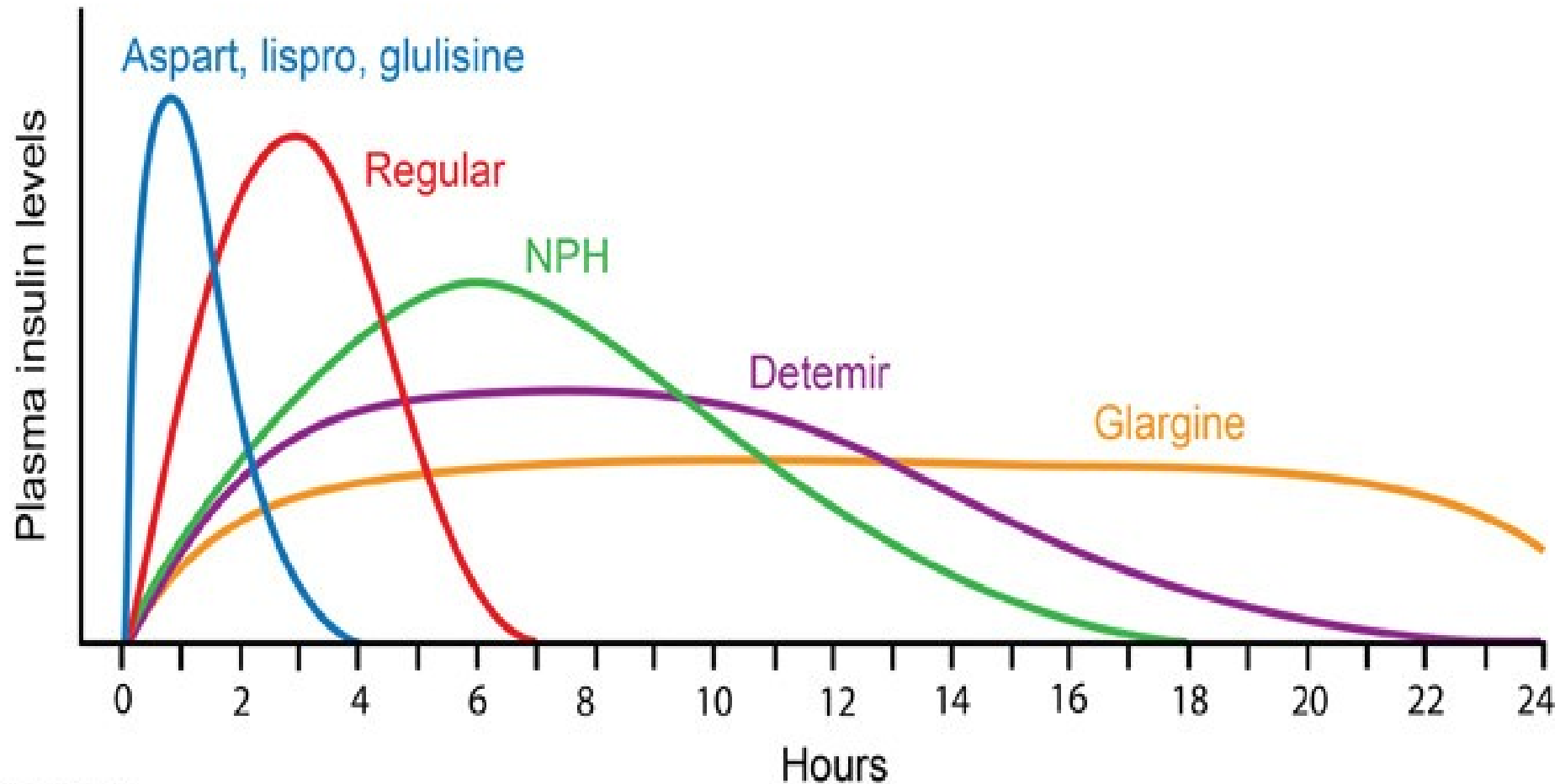


• ***Human insulin (by recombinant DNA technology) has largely replaced that isolated from beef or pork pancreas.***

*The modifications in the **size and composition of the insulin crystals** in the preparations as well as to the **amino acid sequences** of the polypeptides. produced insulins with **different pharmacokinetic** properties.*

Type of preparation	Onset	Peak	Duration
1) <u>Ultrashort Acting</u> Insulin Lispro Insulin Aspart	5-15 min	30-90 minutes	4-6 hrs
2) <u>Short Acting</u> Crystalline Zinc Insulin (soluble, regular)	30-60 min	2-3 hours	6-8 hrs
3) <u>Intermediate Acting</u> Isophane (NPH= neutral protamine hagedorn)	2-4 hours	4-10 hrs	Up to 18 hrs
4) <u>Long Acting</u> Insulin Glargine Insulin Detemir	2-4 hours 1-2 hours	No peak No peak	Up to 24 hrs 16-24 hrs

Pharmacokinetic profiles of common insulin preparations



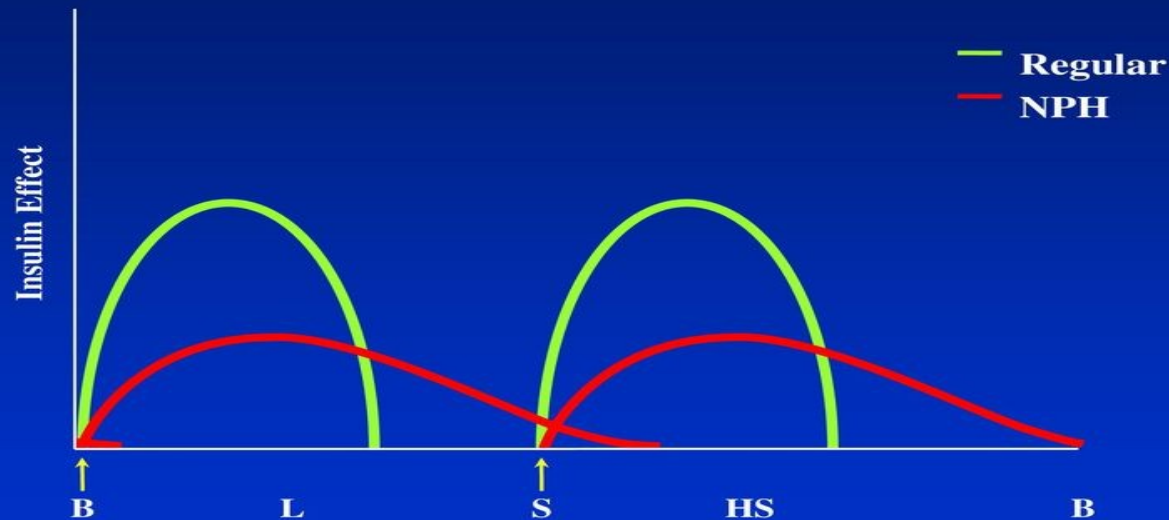
©UWorld

Regimens of insulin therapy

A. Split-mixed regimen: Regular + NPH insulin

dose split to 2 parts; 2/3 given 30 min before breakfast, 1/3 before supper to prevent

Twice-daily Split-mixed Regimens

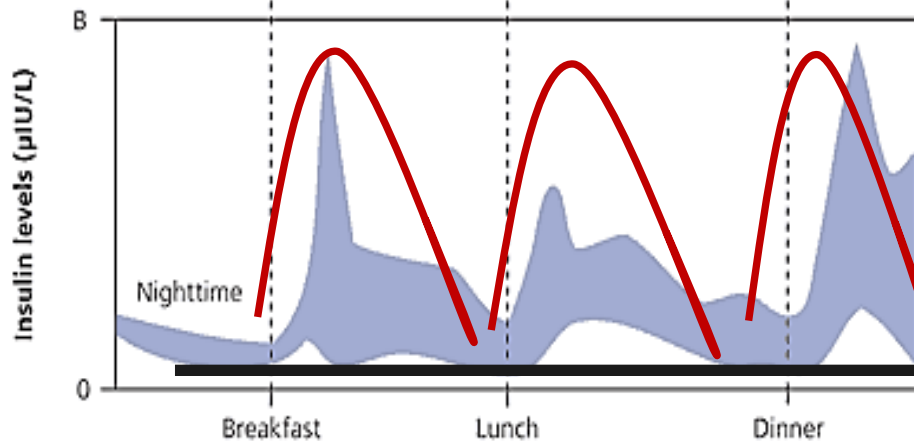


<https://slideplayer.com/slide/12801189/77/images/53/Twice-daily+Split-mixed+Regimens.jpg>

(2) Prandial

insulin(bolus) to control post prandial hyperglycemia

This meal-associated (*prandial*) insulin production is roughly proportional to the amount of carbohydrate in the meal, remaining higher than the basal rate for 1 to 4 hours.



(1) Basal insulin

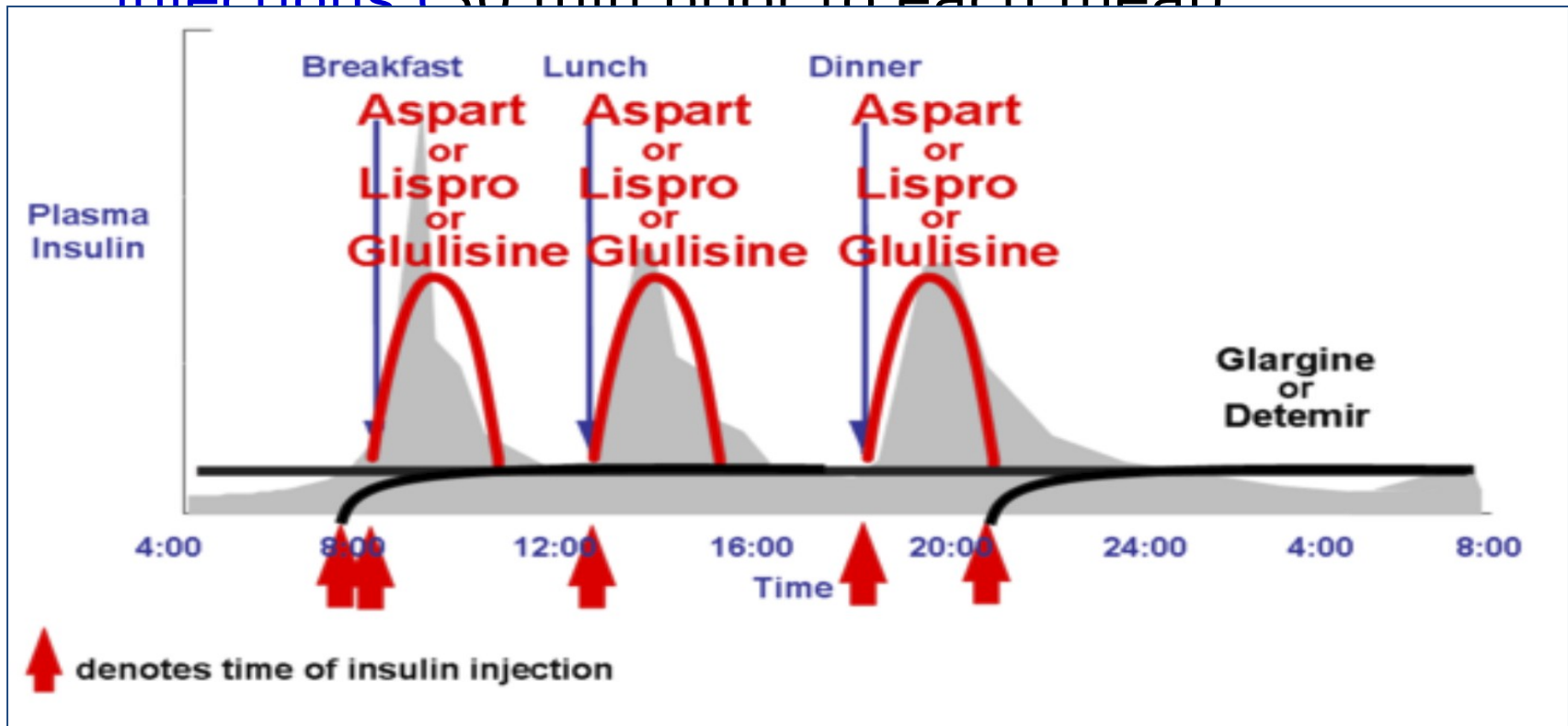
(between meals & ↓ ↓ overnight hepatic glucose production)

**NPH b.i.d. Glargine or
Detemir**

small amounts of insulin into the blood to maintain normal glucose levels

B. Multiple daily injections:

insulin glargine or Detemir given to achieve a more stable basal activity. Regular insulin (or ultra short) must be given in three pre-meals injections (30 min prior to each meal)



<https://encrypted-tbn0.gstatic.com/images?q=tbn%3AANd9GcQS4WB0nqD1km-PukoDpcVRcMh9sYnkOjU9LnVLjGM8L0IwO9MH>

Routes of administration:



Generally administered by **S.C injection**

[**in emergency, injected I.V**]

- **Continuous Subcutaneous *Insulin* infusion pump.**

(does not require multiple injections)

- **Inhaled Aerosol preparation**

(to eliminate the need for injections)

Insulin Pen



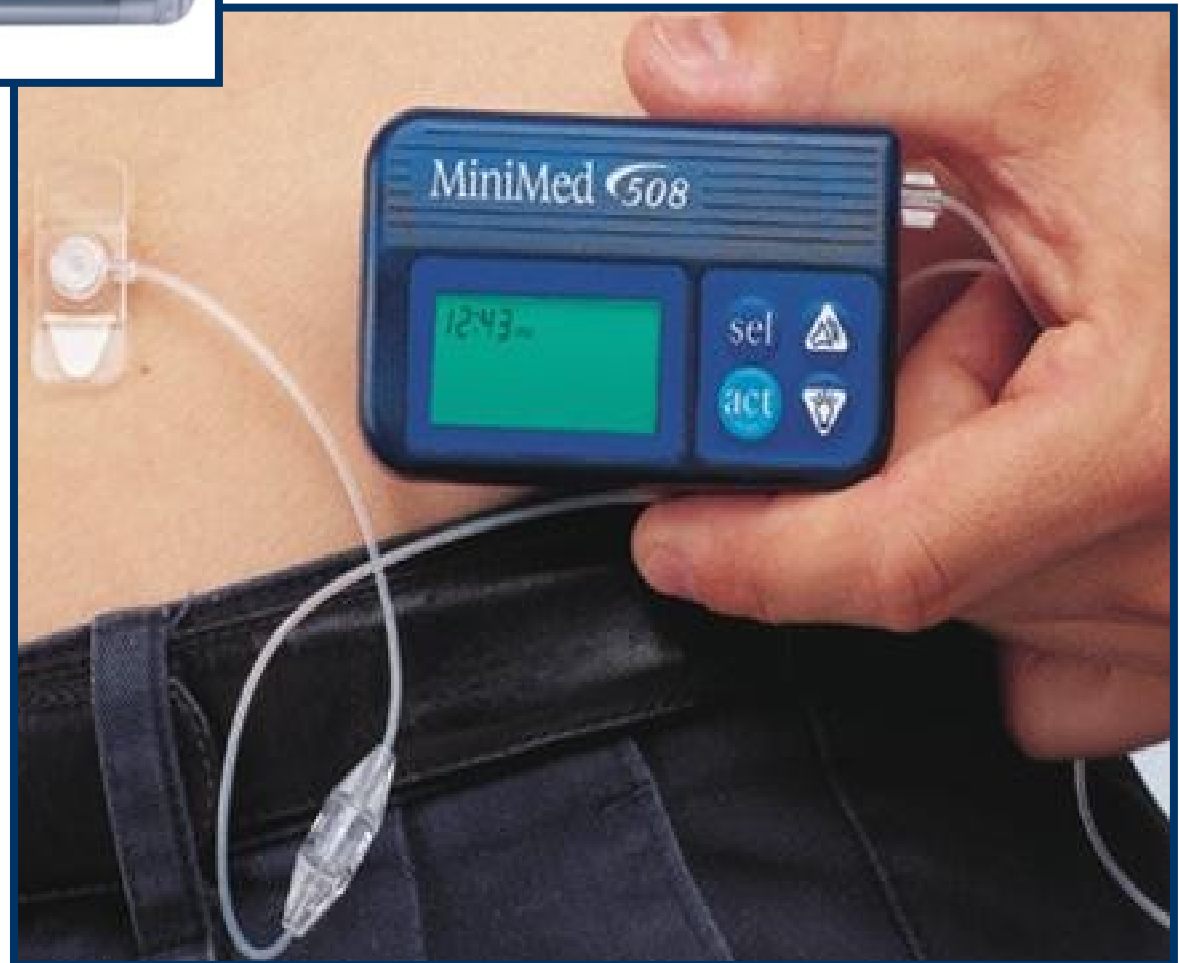
Insulin syringe



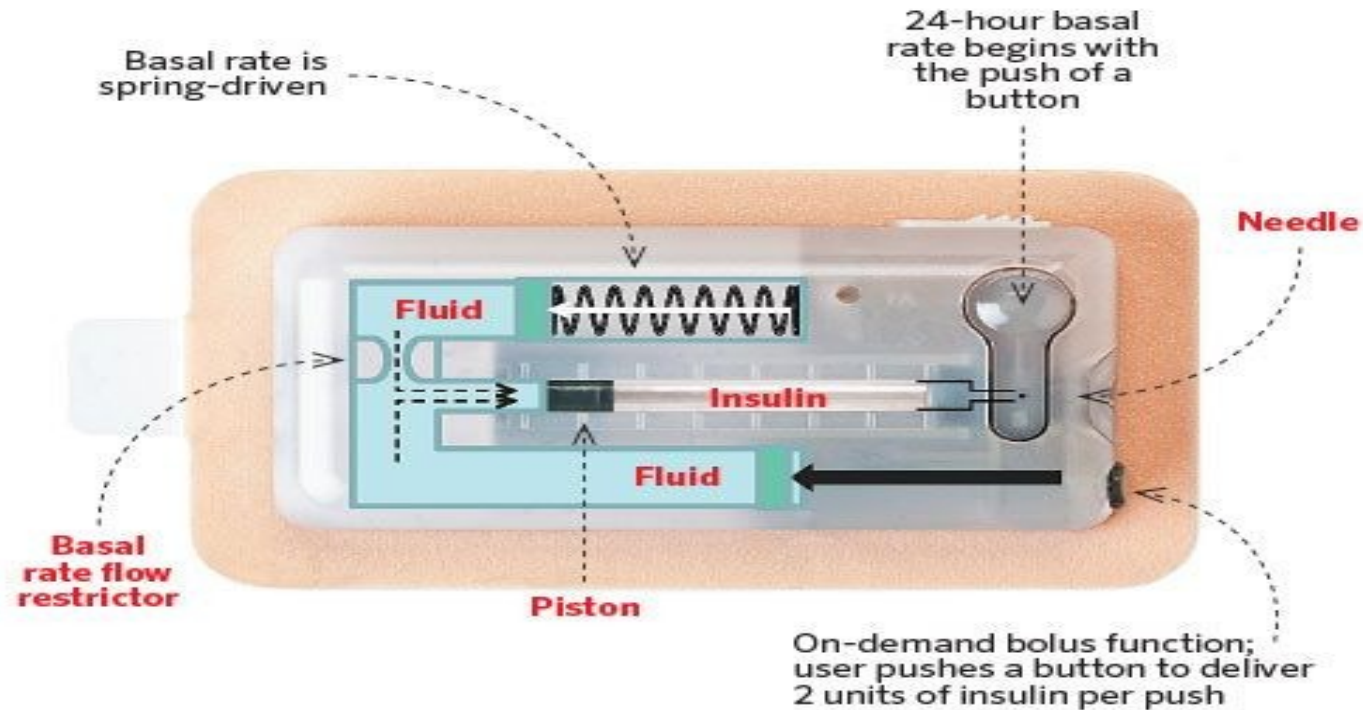
Insulin Pump



Model 715



Insulin Pump



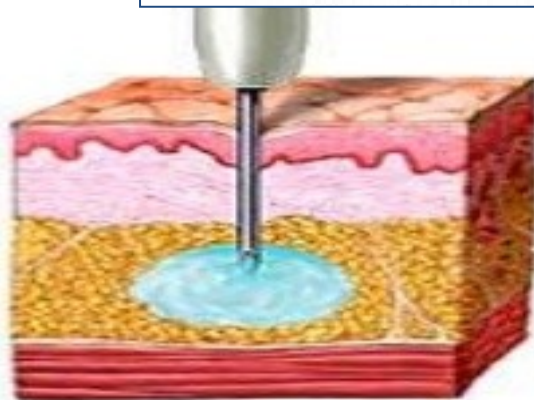
Insulin Pen



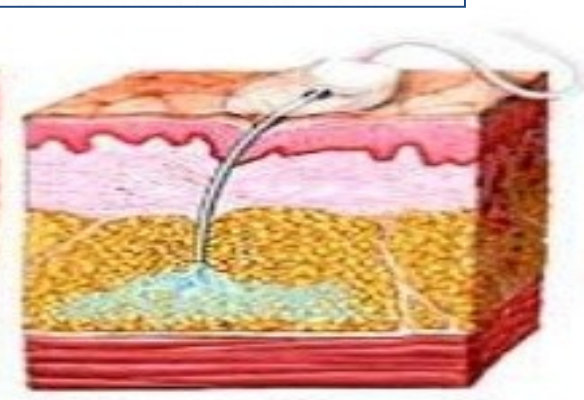
Insulin pumps



Cut-section view of skin



Insulin pen injector



External insulin pump

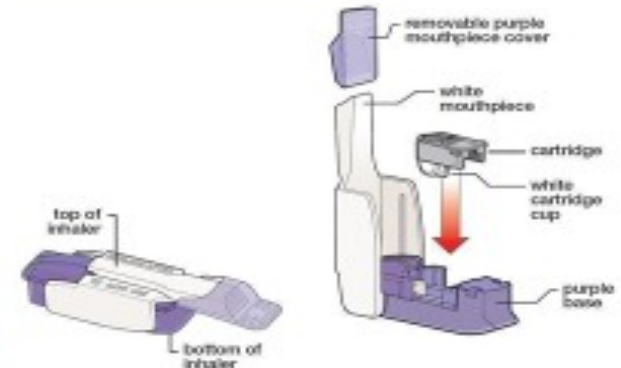
ADAM

Insulin inhalation

Old inhalational preparations



NEW inhalational preparations



Adverse Effects of insulin preparation



1) Hypoglycemia:

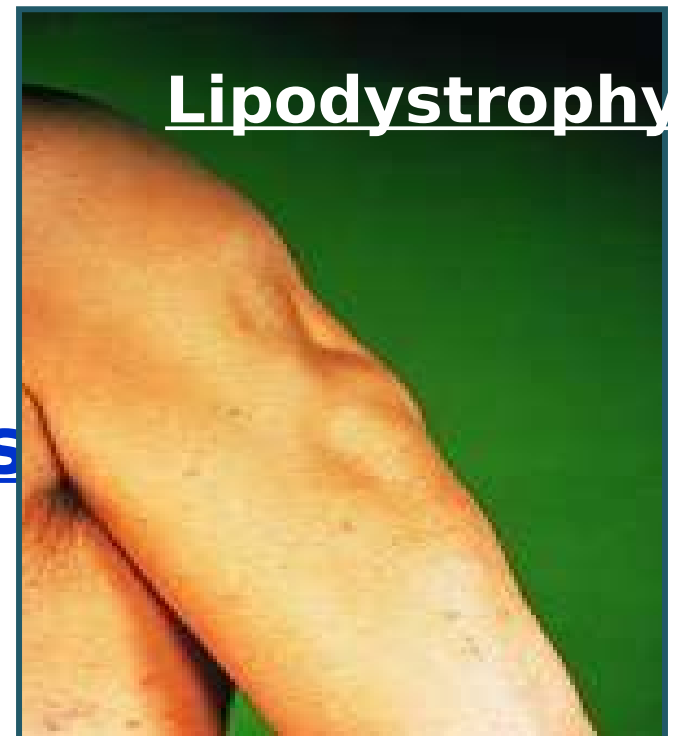
MOST Serious & Common in an overdose

2) Lipodystrophy.

3) Allergic reactions

(less common with human insulin)

4) Hypokalemia





Thank You